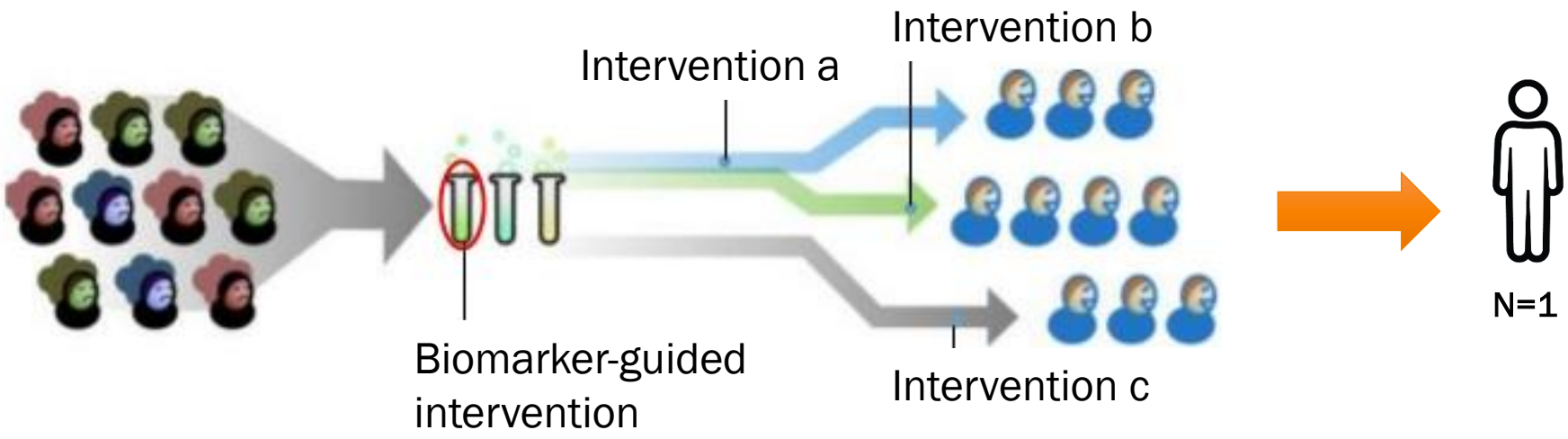
PHENOTYPIC FLEXIBILITY TO QUANTIFY HUMAN VARIABILITY: BUILDING THE BRIDGE TO PERSONALIZED NUTRITION

Dr. S. Wopereis

Outline of presentation

- Introduction to Phenotypic flexibility
- One size fits all: added value of Phenotypic Flexibility
- Responders vs Non-responders: metabotyping
- Personalised nutrition using Phenotypic Flexibility
- Putting all into perspective: added value of phenotypic flexibility for nutrition research



Efficacy quantification from food/nutrition is ‘challenging’

Free living subjects, compliance

Interaction between nutrients

Target population is healthy

Subtle and long term effects

Multiple mechanisms

Inter individual variation

Multiple target tissues

Choice of reference

....ability to adapt and self-manage in the face of social, physical and emotional challenges

BMJ

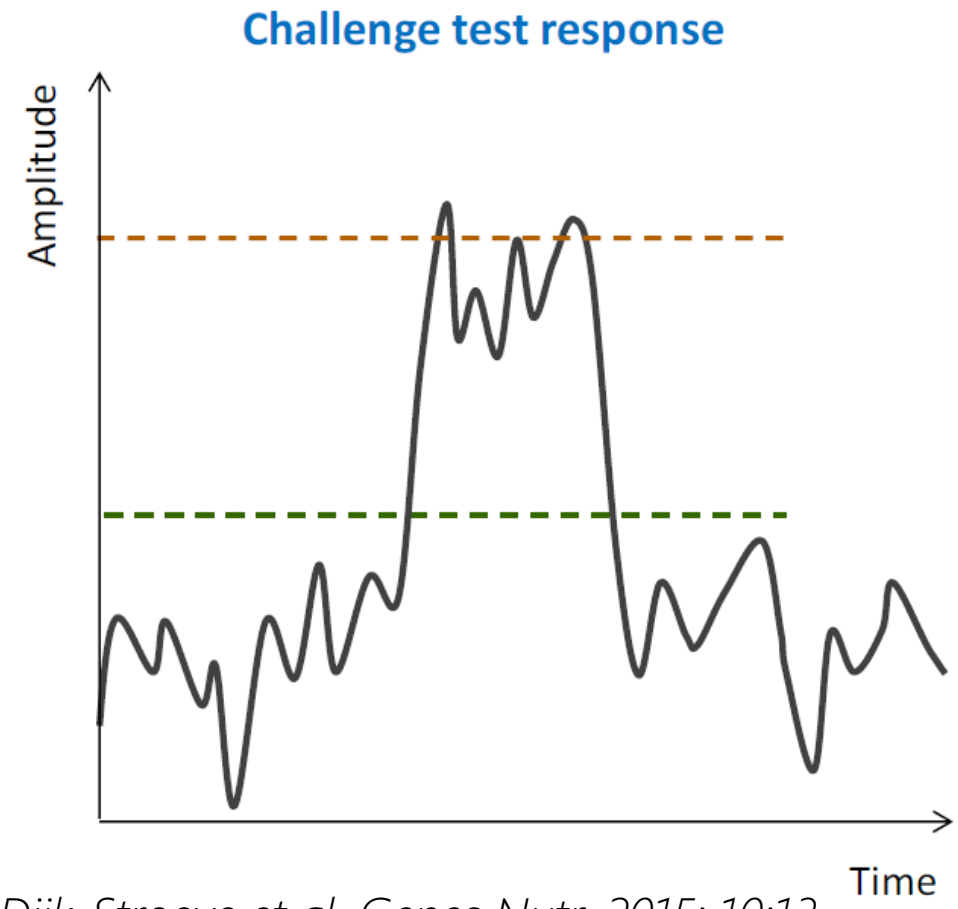
BMJ 2011;343:d4163 doi: 10.1136/bmj.d4163

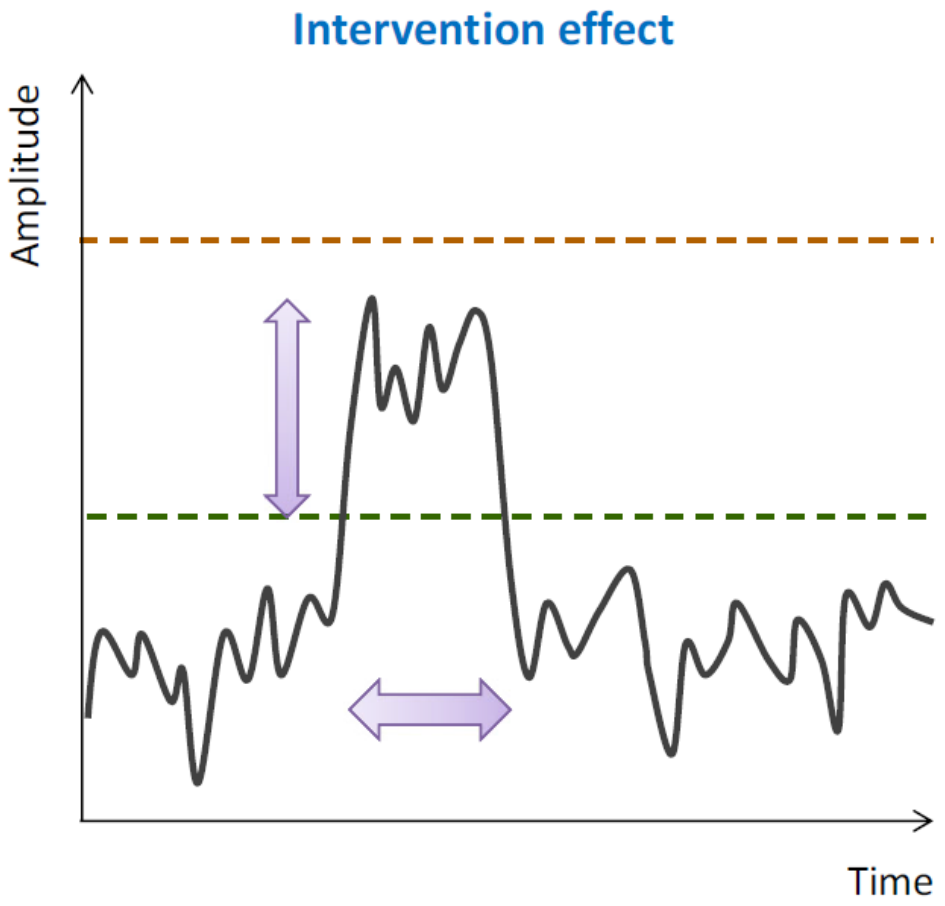
How should we define health?

The WHO definition of health as complete wellbeing is no longer fit for purpose given the rise of chronic disease. **Machteld Huber and colleagues** propose changing the emphasis towards the ability to adapt and self manage in the face of social, physical, and emotional challenges

Machteld Huber *senior researcher*[1], J André Knottnerus *president, Scientific Council for Government Policy* [2], Lawrence Green *editor in chief, Oxford Bibliographies Online—public health*[3], Henriëtte van der Horst *head* [4], Alejandro R Jadad *professor*[5], Daan Kromhout *vice president, Health Council of the Netherlands*[6], Brian Leonard *professor*[7], Kate Lorig *professor*[8], Maria Isabel Loureiro *coordinator for health promotion and protection*[9], Jos W M van der Meer *professor*[10], Paul Schnabel *director* [11], Richard Smith *director*[12], Chris van Weel *head* [13], Henk Smid *director* [14]

The challenge concept:
Study and quantification of the stress response curve



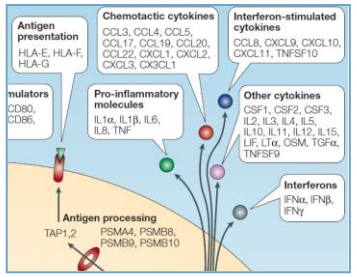


From: Dijk-Stroeve et al. Genes Nutr. 2015; 10:13

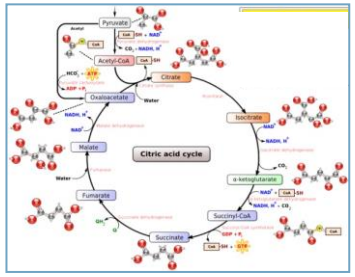
Time course studies to monitor challenge test response

Blood sampling at multiple time before (fasting) and several points after challenge

clinical chemistry



proteome



metabolome

transcriptome

Measuring a broad set of different markers to learn about the effect of food and nutrition on the physiology

Types of challenge test used in nutrition research

- Oral glucose tolerance test (OGTT)
  glucose and insulin metabolism

  e.g. Krug S et al. FASEB J. 2012;26(6):2607-19.

- Oral lipid tolerance test (OLTT)
  fat metabolism

  e.g. Morris et al. Lipids Health Dis. 2015; 14:65.

- Mixed Meal tolerance test (liquid / meal)
  Glucose, Lipid and Protein metabolism

  e.g. Dijk-Stroeve et al. Genes Nutr. 2015;10:13.

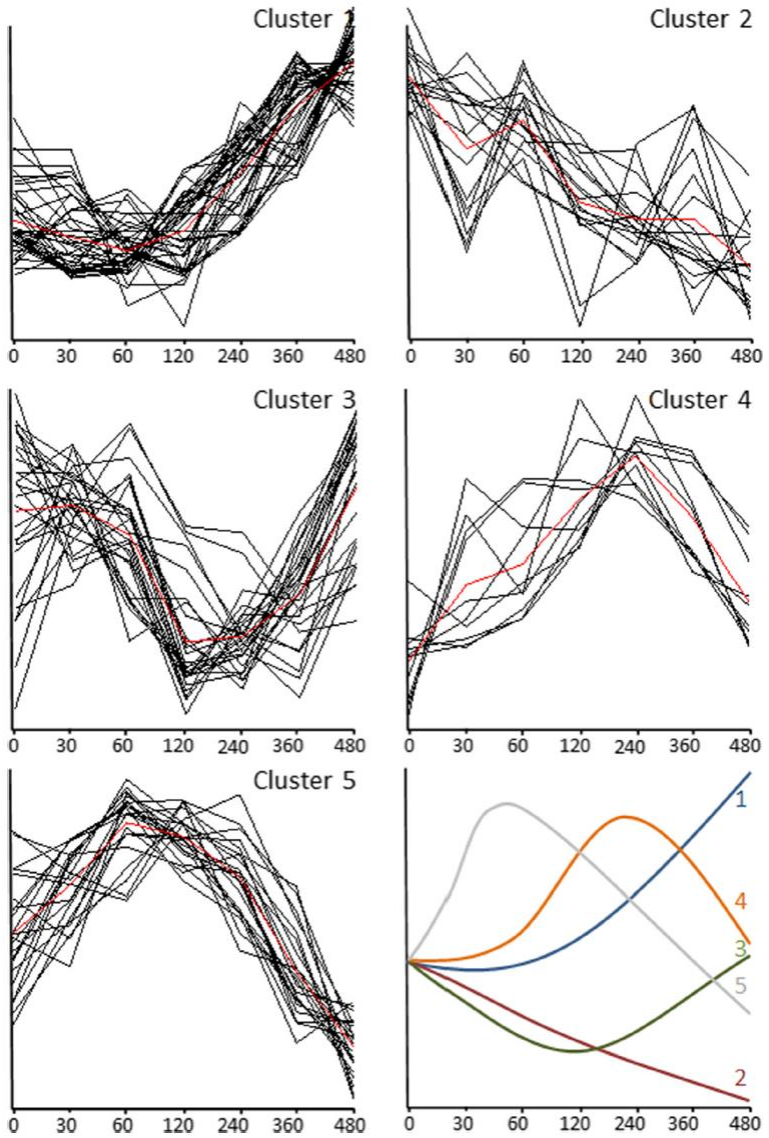
- Prolonged Fasting (i.e. 36 hrs of fasting)
  Catabolic metabolism

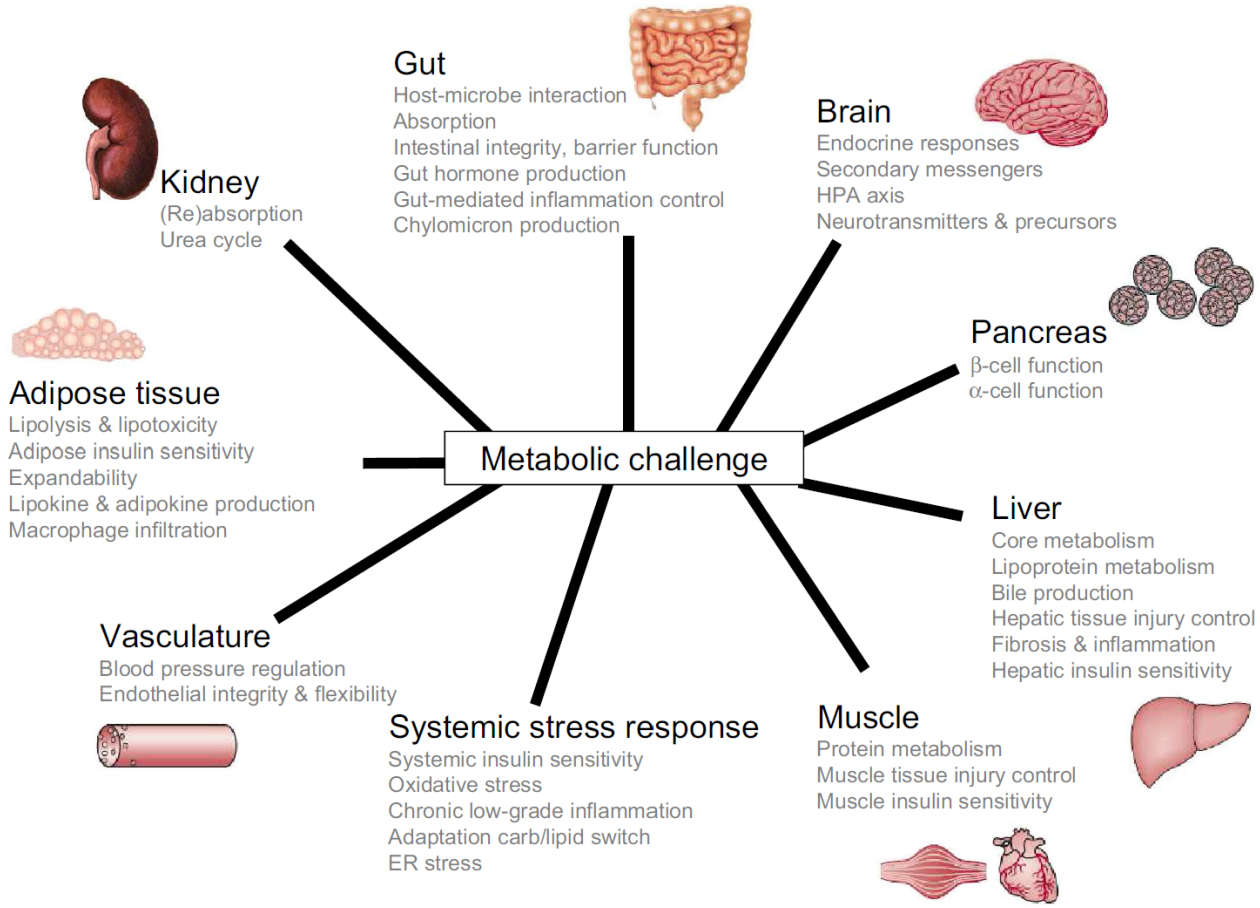
  e.g. Rubio-Aliaga et al. Metabolomics 2011; 7:375-387

- E-coli, Vaccination, Rhinovirus challenge
  (Non-innate) immunity, inflammation

  e.g. Turner RB et al. Benef Microbes 2017; 8(2):207-215;
  van Hoffen et al. Sci Rep (2021); 11(1);6060

Dynamic phenotyping

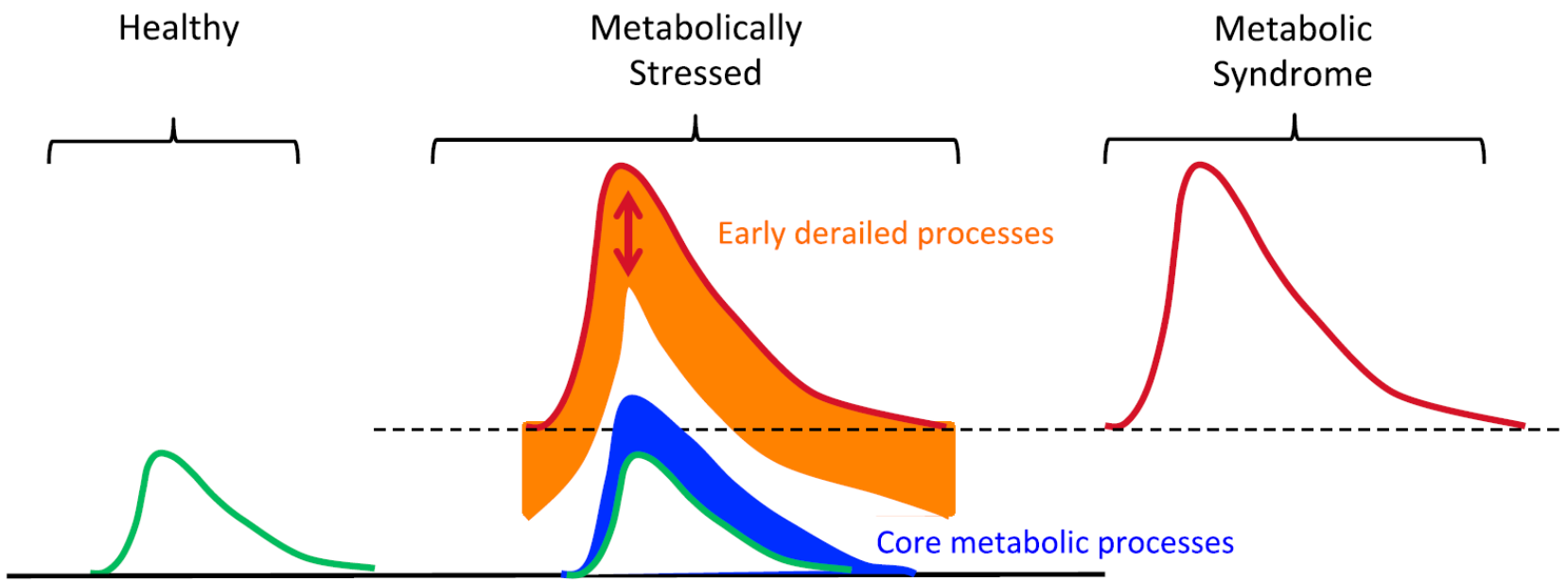


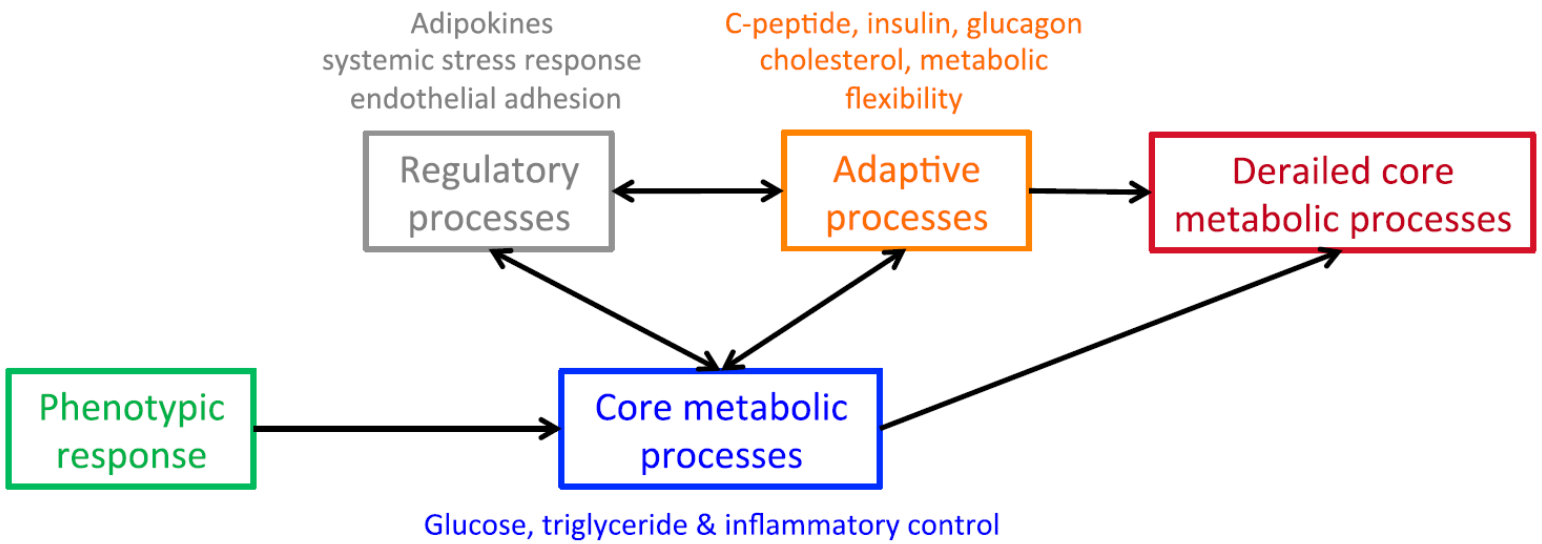


Compare different conditions: i.e. healthy versus diseased; young versus old; lean versus obese and learn from what processes and how metabolic processes are different in terms of dynamics

From: Wopereis et al. Genes Nutr. 2017; 12:21 and Dijk-Stroeve et al. Genes Nutr. 2015; 10:13

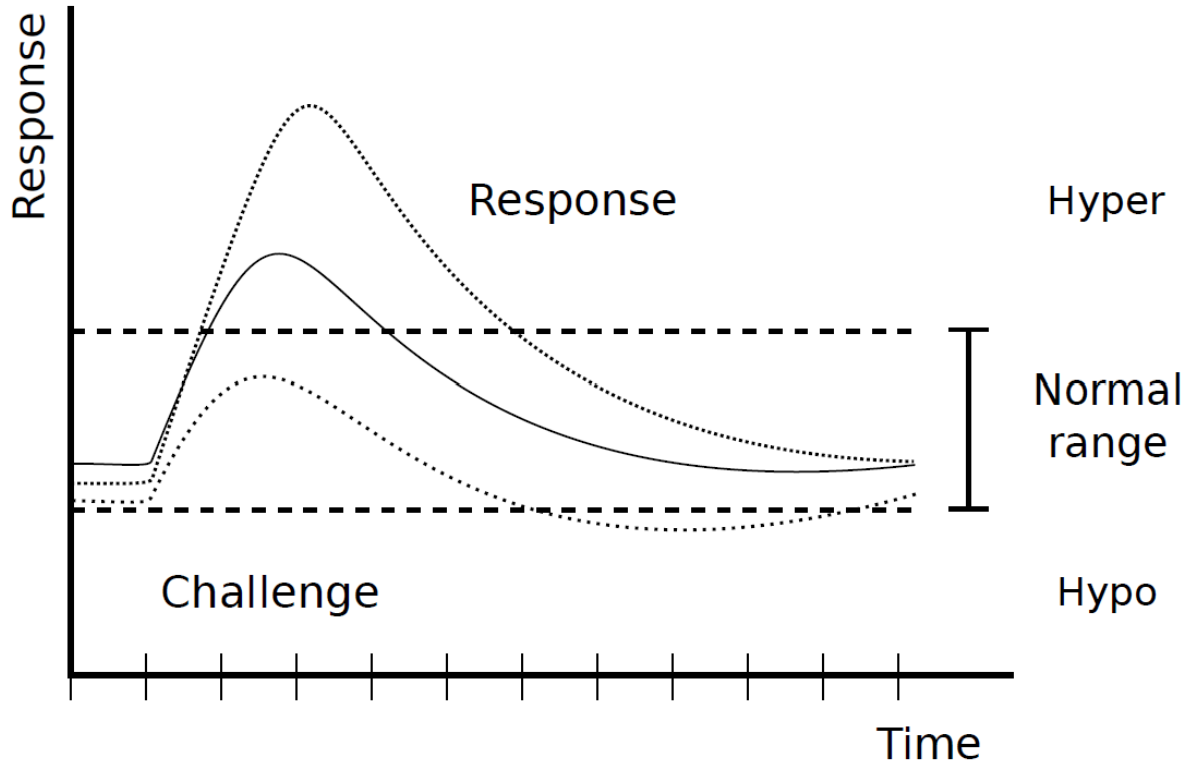
Conceptual framework for derailment of dynamic markers





From: Kardinaal et al. FASEB J. 2015; 29(11):4600-13

Statistical analyses & interpretation



Univariate approach:

1) AUC and kinetic derivatives
2) Linear models with individual time points
3) Kinetic modelling (e.g. PARAFAC)

Multivariate approach:

1) PCA
2) Network analysis
3) PCDA / PLSDA
4) ANOVA Simultaneous Component Analysis (ASCA)
5) Using prior information

Conclusion: not standardised & biological – clinical interpretation remains difficult!

From: Vis et al. Metabolomics 2015; 11:50-63

Can a challenge test quantify health benefits from nutrition?

- 36 overweight healthy male with elevated CRP
  5 weeks supplement mix
  cross-over design placebo vs intervention

Bakker et al. Am J Clin Nutr. 2010; 91:1044-59.
Pellis et al. Metabolomics. 2012; 8(2):347-359.
Bouwman et al. BMC Med Gen. 2012; 6;5:1.

- 10 healthy young male
  before and after 4 weeks overfeeding
  (1300 kcal/day extra)

Kardinaal et al. FASEB J. 2015;29(11):4600-13.

- 18 Metabolic Syndrome (male & female)
  12 weeks High MUFA diet before and after

Cruz-Teno et al. Mol. Nutr. Food Res. 2012;56:854–865

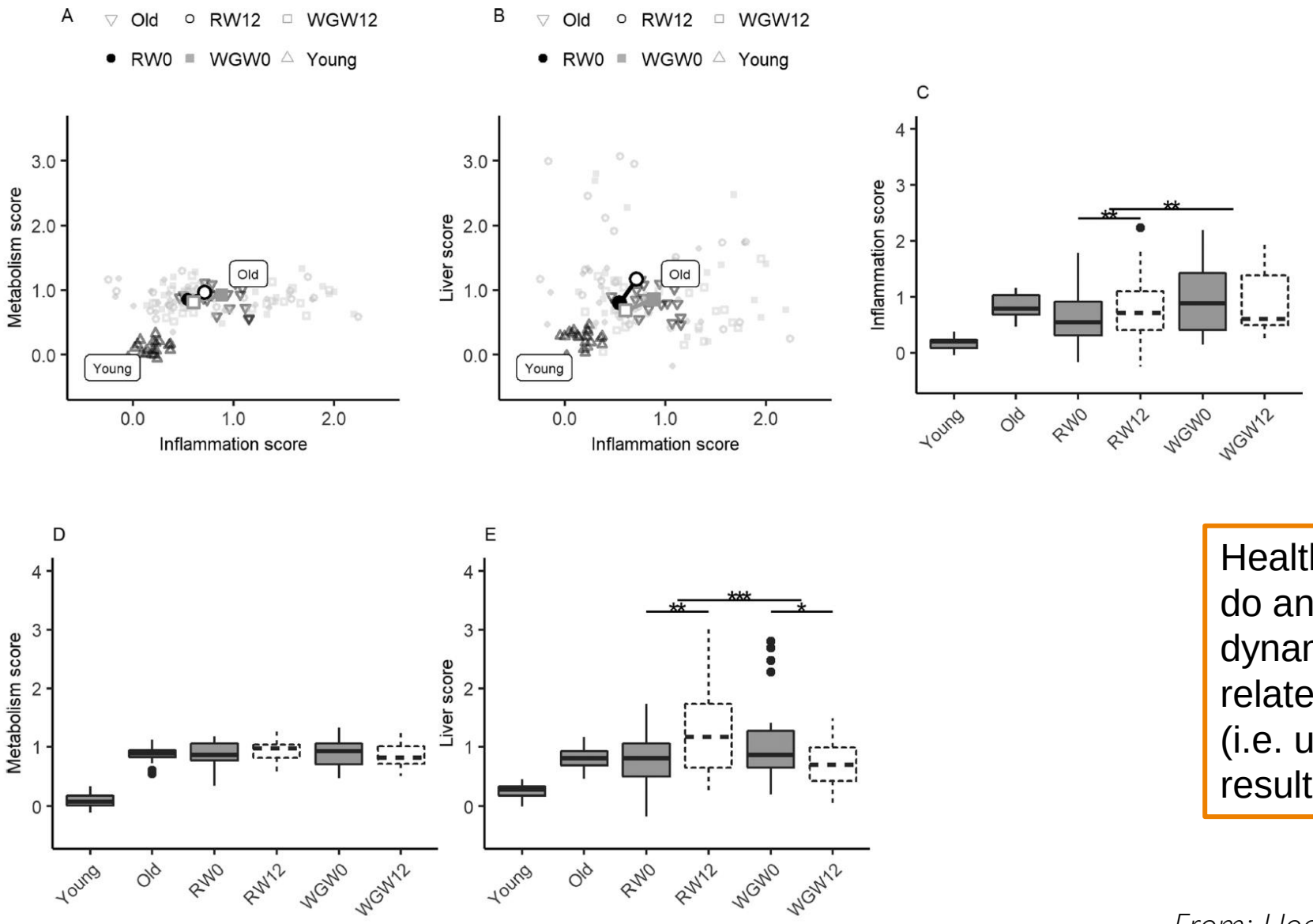
- 29 healthy overweight middle-aged men
  double-blind crossover study
  effects of 4 wk high flavonol chocolate (HFC)
  vs normal dark chocolate (NFC)

Esser et al. FASEB J. 2014;28(3):1464-73

- 50 healthy overweight and obese male and female
  parallel study control vs intervention
  effects of 12 wk whole wheat versus refined wheat

Hoevenaars et al. JoN 2019,149(12):2133-2144

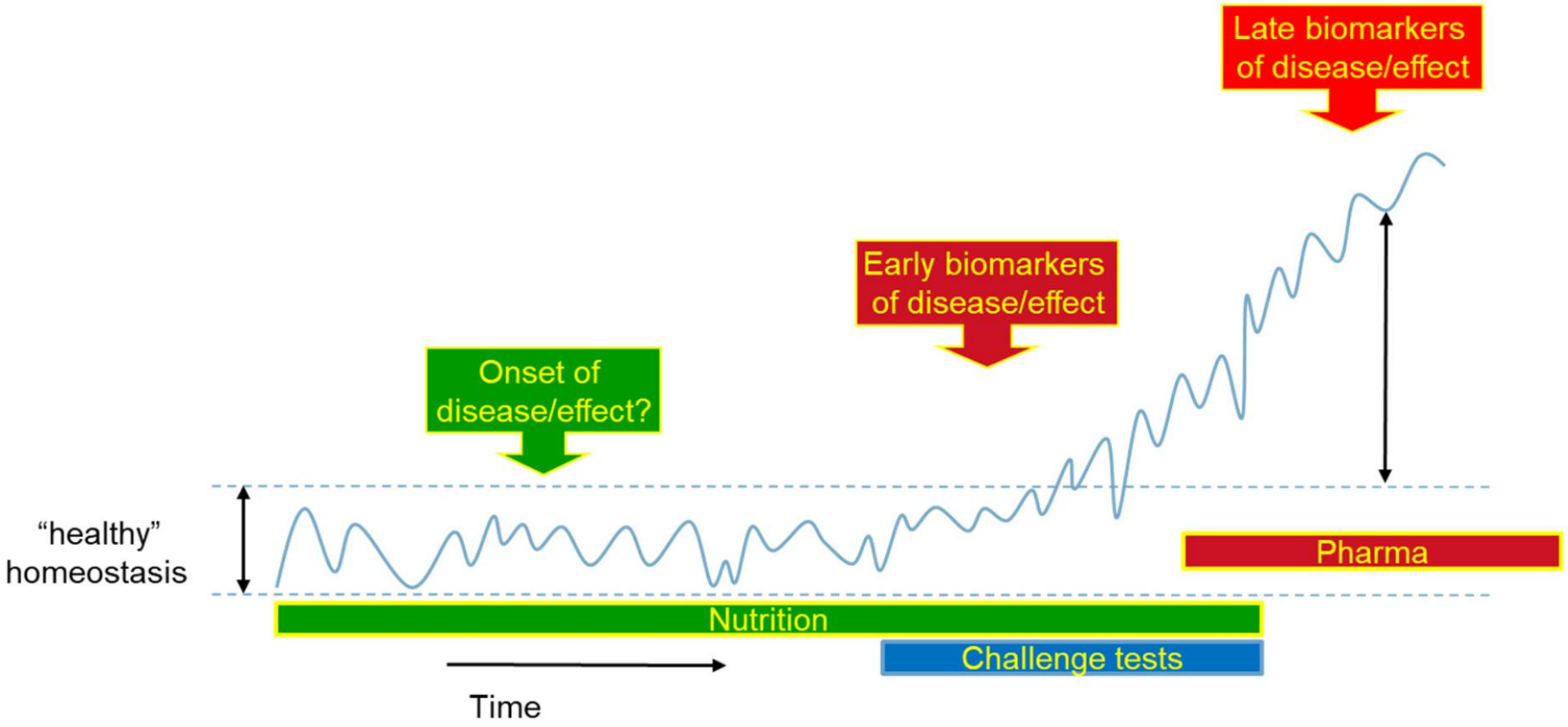
Health space analysis to interpret nutritional intervention effect



Health space analysis may help to do an interpretation of multiple dynamic challenge responses related to separate health domains (i.e. using prior information) as a result from a nutritional intervention.

From: Hoevenaars et al. JoN 2019,149(12):2133-2144

Could phenotypic flexibility lead to a next generation health claims?



Key developments needed:

1) Defined standardised challenge test
2) Defined markers representing benefit area
3) Defined model (i.e. health space) for interpretation
4) Determination of clinical relevance of significant effect

Good news:
In 2017 the EFSA Scientific Committee proposes " increased resilience to a challenge" as a beneficial nutritional health effect

From: Hoevenaars et al. Nutrients 2020, 12(10):2945

ORIGINAL ARTICLE

Weight loss moderately affects the mixed meal challenge response of the plasma metabolome and transcriptome of peripheral blood mononuclear cells in abdominally obese subjects

Parastoo Fazelzadeh[1,5] · Roland W. J. Hangelbroek[1,5] · Peter J. Joris[2,5] · Casper G. Schalkwijk[3] · Diederik Esser[1] · Lydia Afman[1] · Thomas Hankemeier[6] · Doris M. Jacobs[6,7] · Velitchka V. Mihaleva[6,7] · Sander Kersten[1] · John van Duynhoven[4,5,6,7] · Mark V. Boekschoten[1,5]

Received: 27 November 2017 / Accepted: 20 January 2018 / Published online: 5 March 2018

TNO innovation for life

Metabolomics (2018) 14:46

Conclusion We conclude that mixed-meal challenges are not necessarily superior to measurements in the fasted state to assess metabolic health. Furthermore, the mechanisms accounting for the observed differences between lean and abdominally obese in the fasted state are different from those underlying the dissimilarity observed during the postprandial response.

Objectives We examined whether the response to a mixed-meal challenge could provide a readout for a weight loss (WL)-induced phenotype shift in abdominally obese male subjects. The underlying assumption of a mixed meal challenge is that it triggers all aspects of phenotypic flexibility and provokes a more prolonged insulin response, possibly allowing for better differentiation between individuals.

Methods Abdominally obese men (n = 29, BMI = 30.3 ± 2.4 kg/m^2) received a mixed-meal challenge prior to and after an 8-week WL or no-WL control intervention. Lean subjects (n = 15, BMI = 23.0 ± 2.0 kg/m^2) only received the mixed meal challenge at baseline to have a benchmark for WL-induced phenotype shifts.

Results Levels of several plasma metabolites were significantly different between lean and abdominally obese at baseline as well as during postprandial metabolic responses. Genes related to oxidative phosphorylation in peripheral blood mononuclear cells (PBMCs) were expressed at higher levels in abdominally obese subjects as compared to lean subjects at fasting, which was partially reverted after WL. The impact of WL on the postprandial response was modest, both at the metabolic and gene expression level in PBMCs.

Conclusion We conclude that mixed-meal challenges are not necessarily superior to measurements in the fasted state to assess metabolic health. Furthermore, the mechanisms accounting for the observed differences between lean and abdominally obese in the fasted state are different from those underlying the dissimilarity observed during the postprandial response.

Plasma metabolome analysis identifies distinct human metabotypes in the postprandial state with different susceptibility to weight loss–mediated metabolic improvements

Jarlei Fiamoncini,*,[1] Milena Rundle,[†] Helena Gibbons,[‡] Louise Thomas,[§] Kerstin Geillinger-Kästle,* Diana Bunzel,[¶] Jean-Pierre Trezzi,[‖,#] Yoana Kiselova-Kaneva,** Suzan Wopereis,[††] Judith Wahrheit,[‡‡] Sabine E. Kulling,[¶] Karsten Hiller,[§§,¶¶] Denise Sonntag,[††] Diana Ivanova,** Ben van Ommen,[††] Gary Frost,[†] Lorraine Brennan,[‡] Jimmy Bell,[§] and Hannelore Daniel*

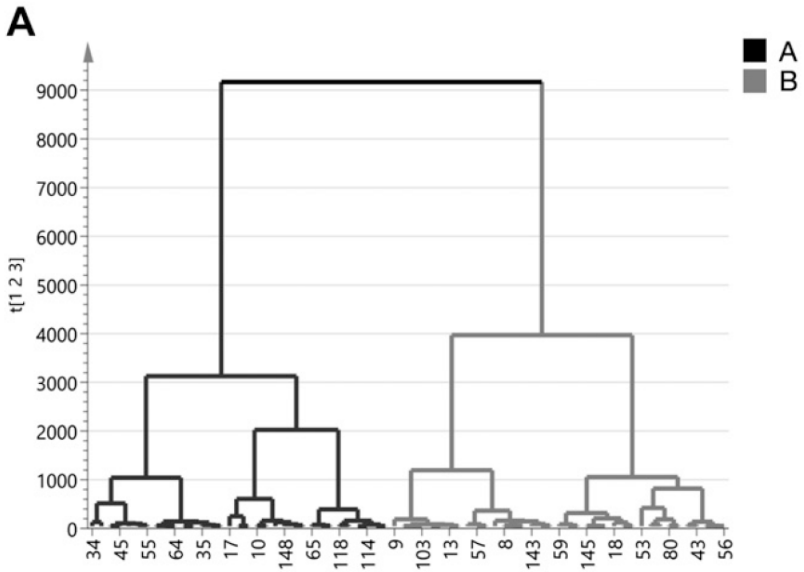
*Department Food and Nutrition, Technische Universität München, Freising-Weihenstephan, Germany; [†]Division of Diabetes, Endocrinology and Metabolism, Department of Medicine, Imperial College London, London, United Kingdom; [‡]University College Dublin (UCD) School of Agriculture and Food Science, Institute of Food and Health, Dublin, Ireland; [§]Research Centre for Optimal Health, Department of Life Sciences, University of Westminster, London, United Kingdom; [¶]Department of Safety and Quality of Fruit and Vegetables, Max Rubner Institut, Karlsruhe, Germany; [‖]Integrated Biobank of Luxembourg, Dudelange, Luxembourg; [#]Centre for Systems Biomedicine, Esch-sur-Alzette, Luxembourg; **Department of Biochemistry, Molecular Medicine and Nutrigenomics, Medical University Varna, Varna, Bulgaria; [††]Department of Microbiology and Systems Biology, Netherlands Institute for Applied Scientific Research (TNO), Zeist, The Netherlands; [‡‡]Biocrates Life Sciences, Innsbruck, Austria; and [§§]Braunschweig Integrated Centre of Systems Biology, University of Braunschweig, Braunschweig, Germany; and [¶¶]Department of Computational Biology of Infection Research, Helmholtz Centre for Infection Research, Braunschweig, Germany

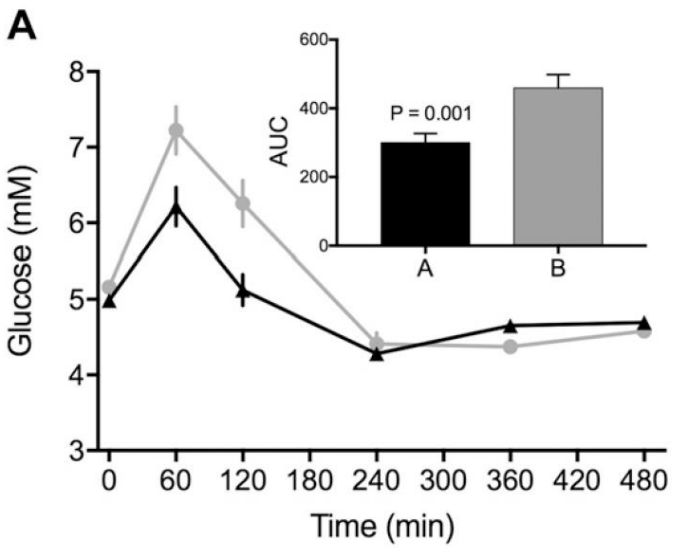
ABSTRACT: Health has been defined as the capability of the organism to adapt to challenges. In this study, we tested to what extent comprehensively phenotyped individuals reveal differences in metabolic responses to a standardized mixed meal tolerance test (MMTT) and how these responses change when individuals experience moderate weight loss. Metabolome analysis was used in 70 healthy individuals. with profiling of ~300 plasma metabolites during an MMTT over 8 h. Multivariate analysis of plasma markers of fatty acid catabolism identified 2 distinct metabotype clusters (A and B). Individuals from metabotype B showed slower glucose clearance, had increased intra-abdominal adipose tissue mass and higher hepatic lipid levels when compared with individuals from metabotype A. An NMR-based urine analysis revealed that these individuals also to have a less healthy dietary pattern. After a weight loss of ~5.6 kg over 12 wk, only the subjects from metabotype B showed positive changes in the glycemic response during the MMTT and in markers of metabolic diseases. Our study in healthy individuals demonstrates that more comprehensive phenotyping can reveal discrete metabotypes with different outcomes in a dietary intervention and that markers of lipid catabolism in plasma could allow early detection of the metabolic syndrome.—Fiamoncini, J., Rundle, M., Gibbons, H., Thomas, L., Geillinger-Kästle, K., Bunzel, D., Trezzi, J-P., Kiselova-Kaneva, Y., Wopereis, S., Wahrheit, J., Kulling, S. E., Hiller, K., Sonntag, D., Ivanova, D., van Ommen, B., Frost, G., Brennan, L., Bell, J. Daniel, H. Plasma metabolome analysis identifies distinct human metabotypes in the postprandial state with different susceptibility to weight loss–mediated metabolic improvements. FASEB J. 32, 000–000 (2018).

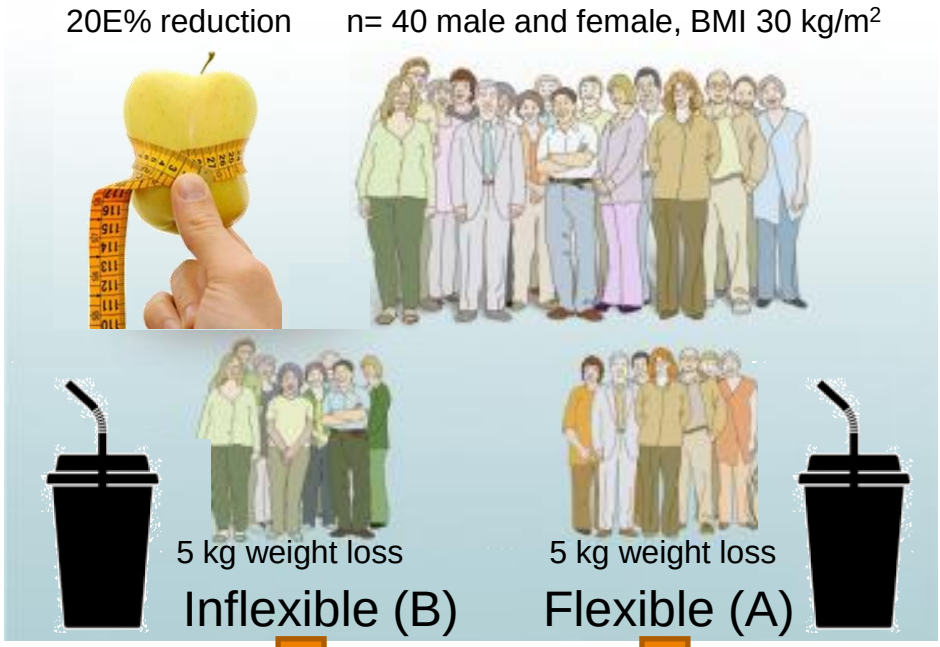
TNO innovation for life

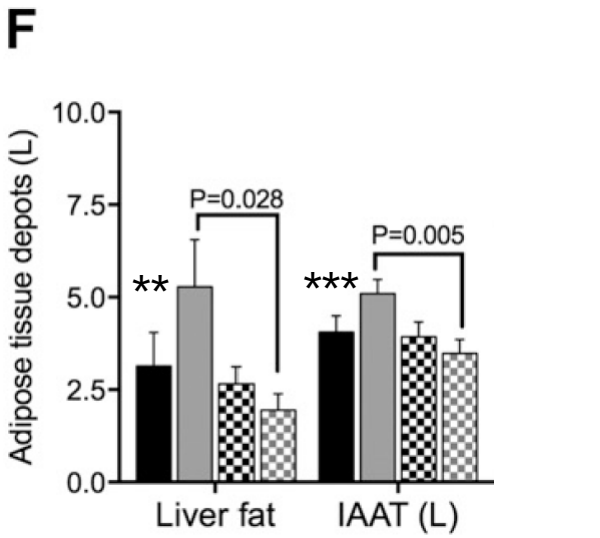
FASEB J (2018) 32(10):5447-5458

Metabotypes represented responders and non-responders to weight loss health benefit









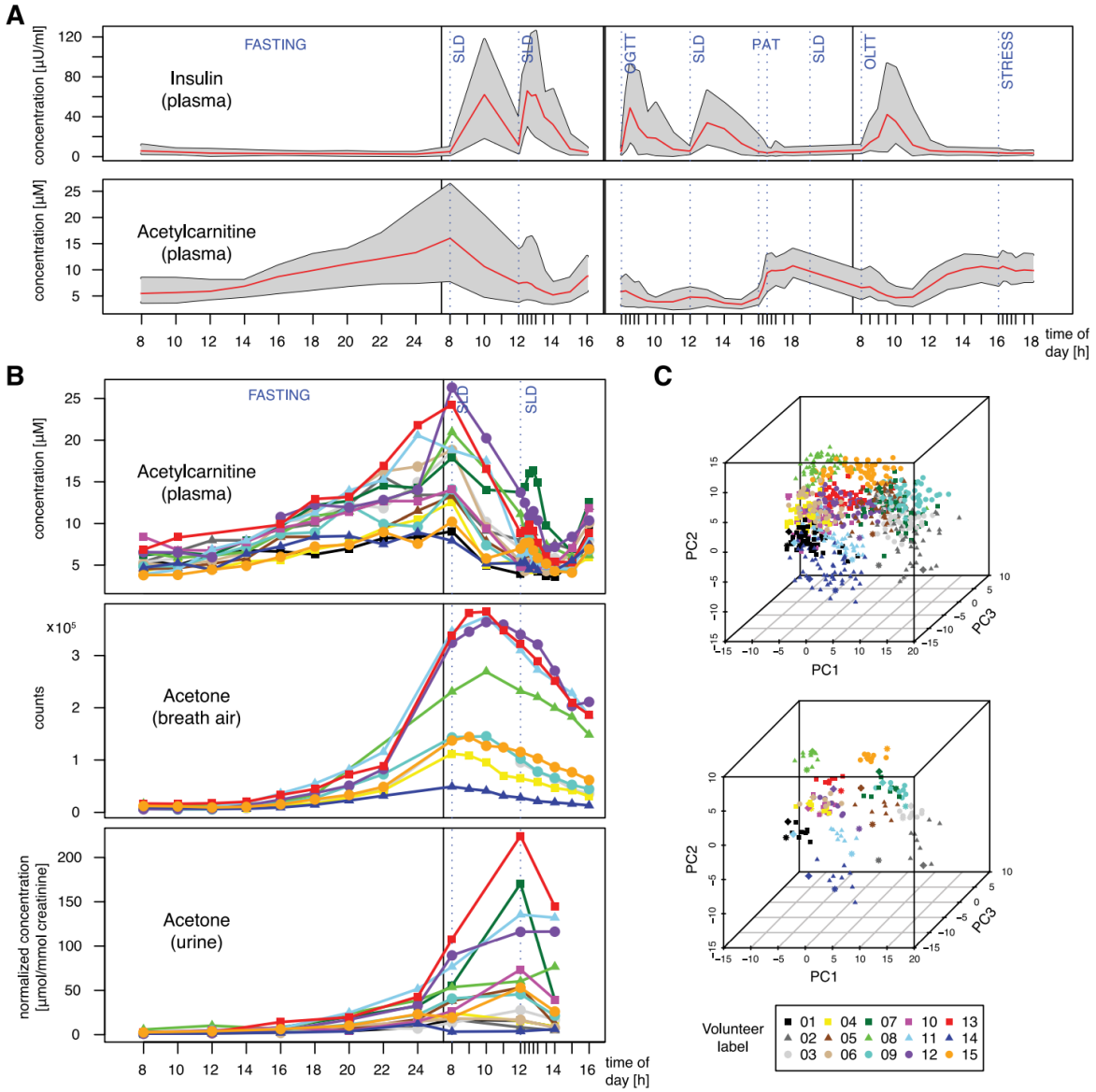
urine sampling for dietary pattern analysis

Inflexible (B)	Flexible (A)
• 42%	• 73%
• higher	• Higher

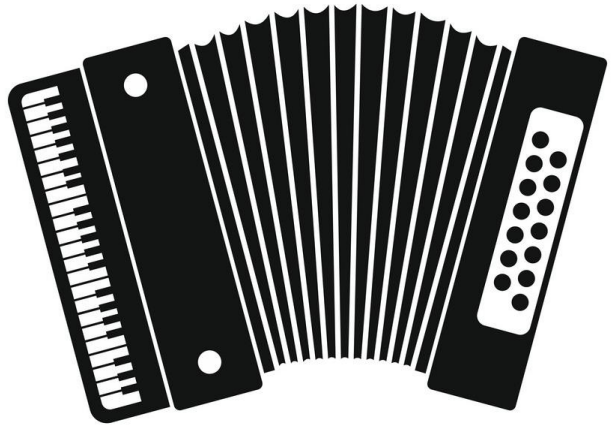
Adapted from: Fiamoncini et al. FASEB J 2018; 32(10):5447-5458

Towards personalised nutrition…

N=15 healthy male Caucasians within narrow BMI and age range



"Interindividual variation can be extended and compressed by metabolic challenges: the accordion effect"



V13 & V14 may be related to the individual's metabolic capacity in utilisation of fatty acids; strong correlation with C2/C16 carnitine ratio

From: Krug et al. FASEB J 2012; 26(6):2607-19

Hallmark PREDICT study came to the same conclusion

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-020-0934-0

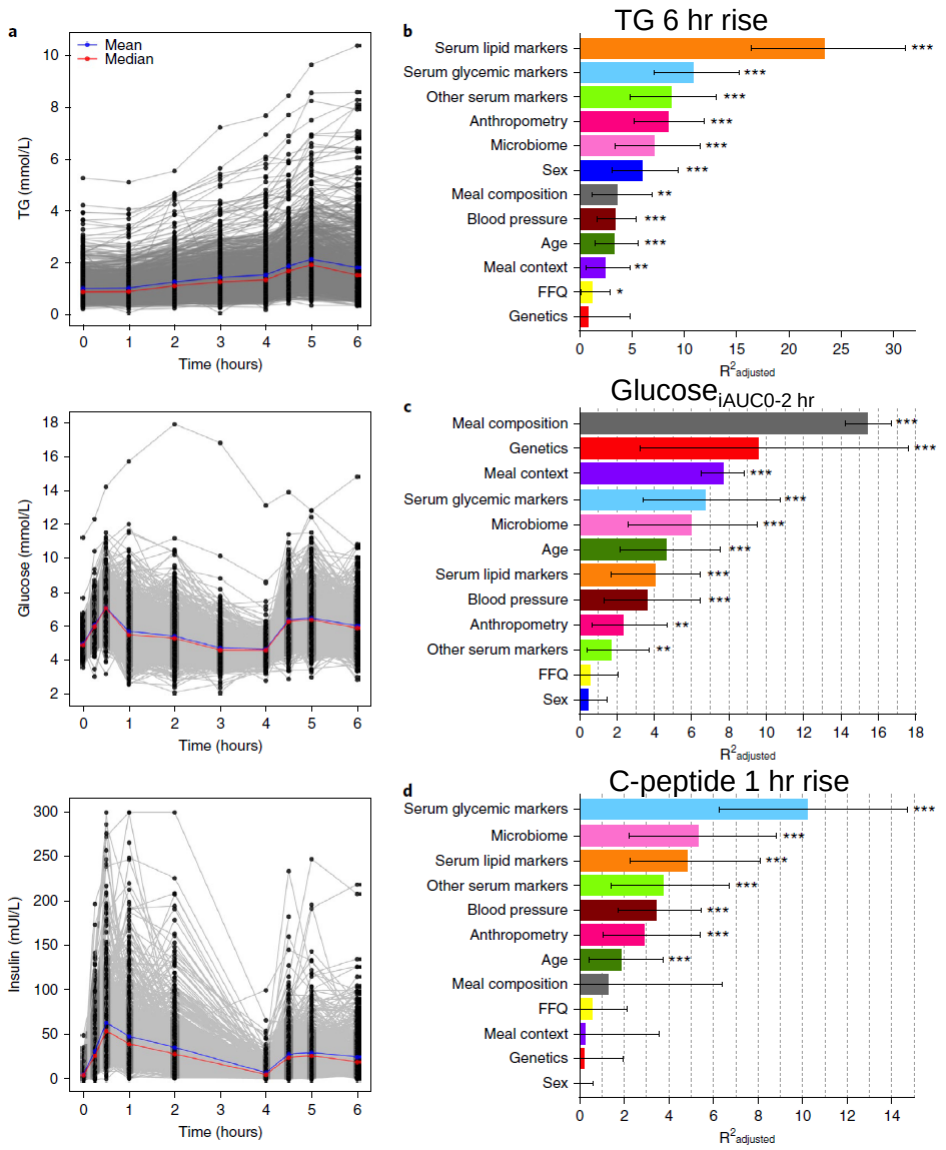
Check for updates

Human postprandial responses to food and potential for precision nutrition

Sarah E. Berry[1,15], Ana M. Valdes[2,3,15] ✉, David A. Drew[4], Francesco Asnicar[5], Mohsen Mazidi[6], Jonathan Wolf[7], Joan Capdevila[7], George Hadjigeorgiou[7], Richard Davies[7], Haya Al Khatib[1,7], Christopher Bonnett[7], Sajaysurya Ganesh[7], Elco Bakker[7], Deborah Hart[6], Massimo Mangino[6], Jordi Merino[4,8,9], Inbar Linenberg[7], Patrick Wyatt[7], Jose M. Ordovas[10,11], Christopher D. Gardner[12], Linda M. Delahanty[4], Andrew T. Chan[4], Nicola Segata[5,15], Paul W. Franks[6,13,14,15] and Tim D. Spector[6,15] ✉

Metabolic responses to food influence risk of cardiometabolic disease, but large-scale high-resolution studies are lacking. We recruited $n = 1,002$ twins and unrelated healthy adults in the United Kingdom to the PREDICT 1 study and assessed postprandial metabolic responses in a clinical setting and at home. We observed large inter-individual variability (as measured by the population coefficient of variation (s.d./mean, %)) in postprandial responses of blood triglyceride (103%), glucose (68%) and insulin (59%) following identical meals. Person-specific factors, such as gut microbiome, had a greater influence (7.1% of variance) than did meal macronutrients (3.6%) for postprandial lipemia, but not for postprandial glycemia (6.0% and 15.4%, respectively); genetic variants had a modest impact on predictions (9.5% for glucose, 0.8% for triglyceride, 0.2% for C-peptide). Findings were independently validated in a US cohort ($n = 100$ people). We developed a machine-learning model that predicted both triglyceride ($r = 0.47$) and glycemic ($r = 0.77$) responses to food intake. These findings may be informative for developing personalized diet strategies. The ClinicalTrials.gov registration identifier is NCT03479866.

N=1002 participants (UK), of which n=183 monozygotic and n=47 dizygotic twins. Validated in n=100 USA



From: Berry et al. Nat Med. 2020;26(6):964-973.

First personalised nutrition study based on phenotypic flexibility

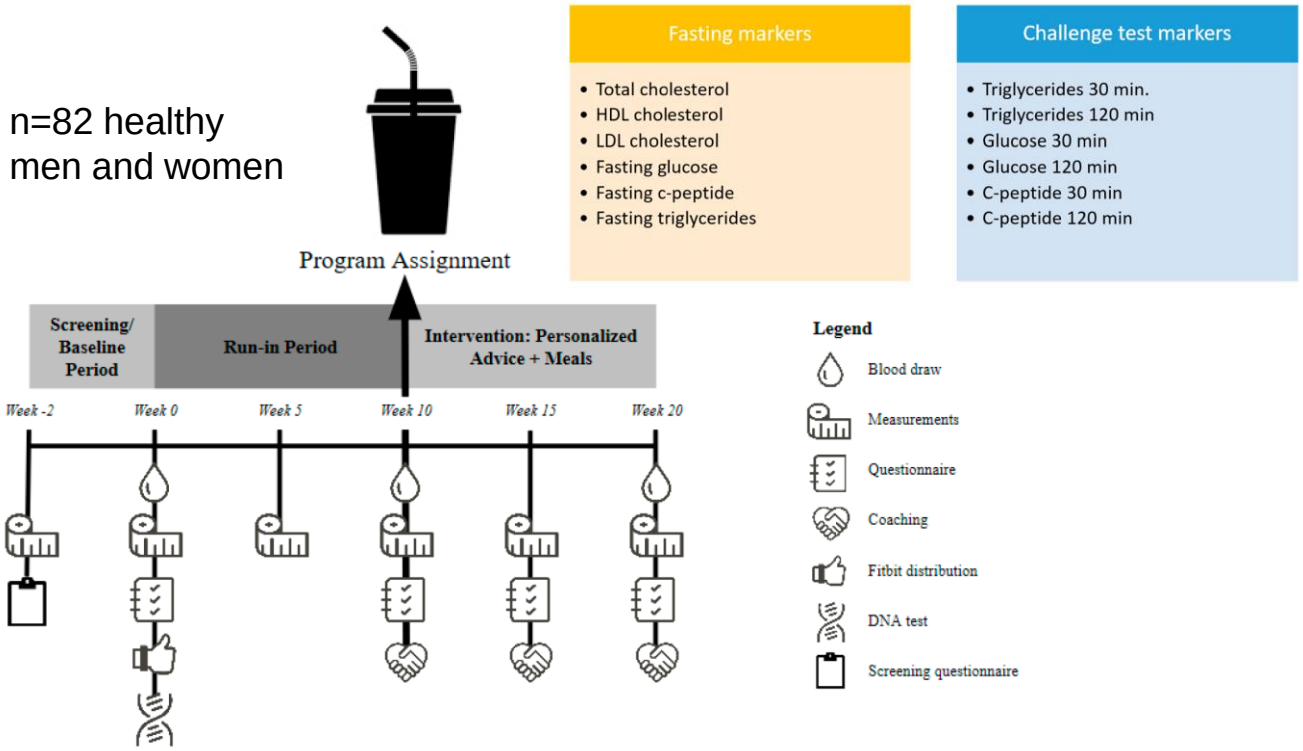
nutrients

MDPI

Article

A Novel Personalized Systems Nutrition Program Improves Dietary Patterns, Lifestyle Behaviors and Health-Related Outcomes: Results from the Habit Study

Iris M. de Hoogh [1], Barbara L. Winters [2], Kristin M. Nieman [3], Sabina Bijlsma [1], Tanja Krone [1], Tim J. van den Broek [1], Barbara D. Anderson [4], Martien P. M. Caspers [1], Joshua C. Anthony [5,6,†] and Suzan Wopereis [1,*]

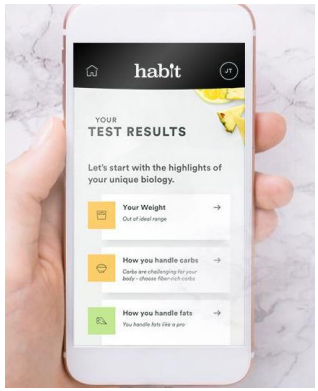


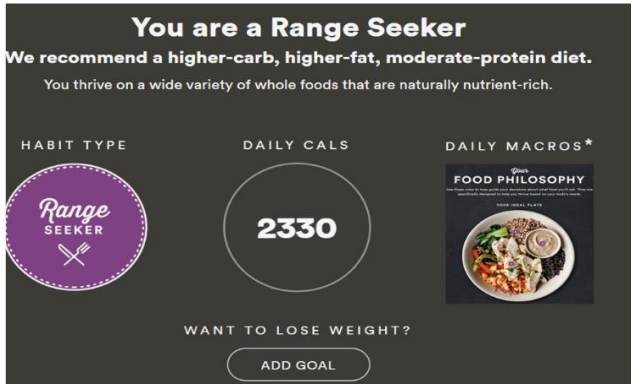
"This study shows that a Personalised Systems Nutrition program in a workforce improves lifestyle habits and reduces body weight, BMI and other health-related outcomes. Health improvement was most pronounced in the compromised phenotypic flexibility subgroup, which indicates that Personalised Systems Nutrition program may be effective in targeting behavior change in health-compromised target groups"

From: de Hoogh et al. Nutrients 2021;13(6):1763

The personalised Systems Nutrition Program used in Habit study

Advice category	Personalized Advice	Personalization factor	Personalization based on SNP
Personalized Diet types & SNP-based macronutrient advice	Protein intake	Glucose tolerance, disposition index, BP	FTO
	Carbohydrate intake	WC, 2-h glucose	FTO, ADAMTS9, GCKR
Micronutrient advice	Fiber intake	Fasting glucose, 2-h glucose, LDL cholesterol, BP, WC	ADAMTS9, TCF7L2
	MUFA intake	Disposition index, LDL, BP, fasting and postprandial TG	-
	Omega-3 intake	BP, fasting and postprandial TG, n-3 index	FADS1





Adapted from: de Hoogh et al. Nutrients 2021;13(6):1763

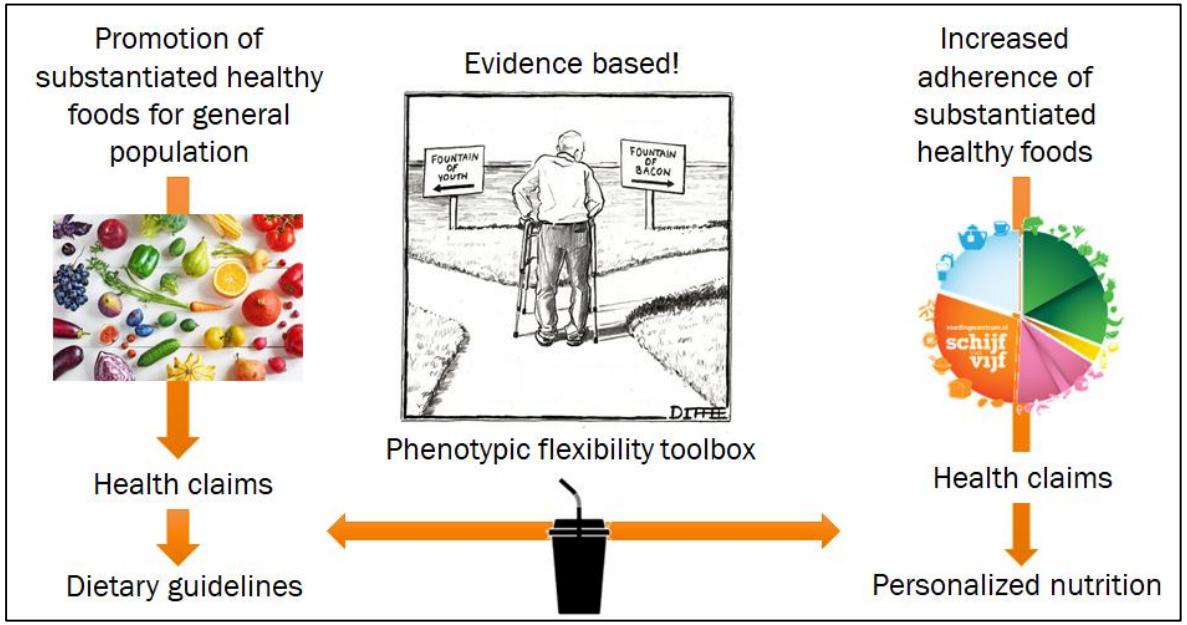
What is the potential of phenotypic flexibility for the nutrition field?

Next generation of health claims

Extension of interindividual variation

Individual diagnosis of health state

Composite resilience biomarkers



Substantiation of health benefits from food and nutrition

Bridge to personalised nutrition

Biomarkers of health instead of disease

Early detection of health derailment

Detection of metabotypes

Stratification of responders and non-responders

Adapted from: Griffiths et al. Eur J Nutr 2020;59(Suppl 2):11-23.


THANK YOU FOR
YOUR TIME
TNO innovation for life